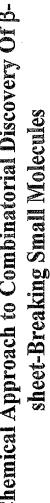
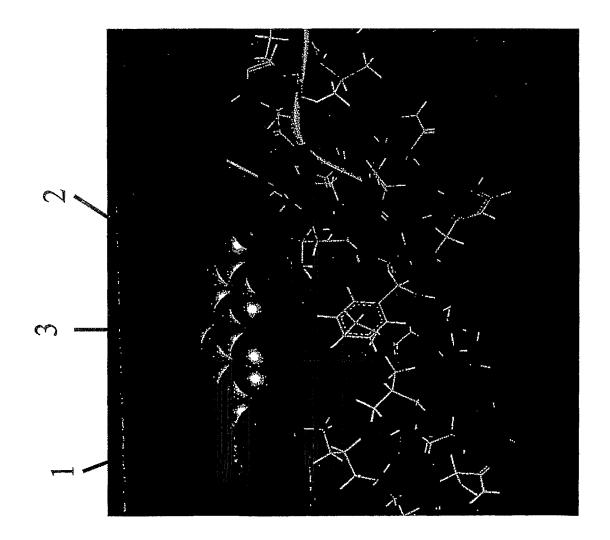
FIGURE 1

Chemical Approach to Combinatorial Discovery Of B-



- by selective electrostatic 1 - Helix stabilization interactions
- via interaction with the rigid hydrophobic scaffold • 2 – Helix stabilization
- 3 Combinatorially varied substituents



SUBSTITUTE SHEET (RULE 26)

"Morphomer" concept

FIGURE 2

• Molecular scaffolds are designed complementary to $A\beta$ helical (soluble) structure

 Conformational restrictions are introduced to partially lock each set of conformations (morphology) of library components • Libraries formed on the basis of scaffolds explore both chemical (Rx) and conformational diversity space

FIGURE 3

Molecular Adaptation of Morphomers to the Target Leads to Formation of Stronger Complexes

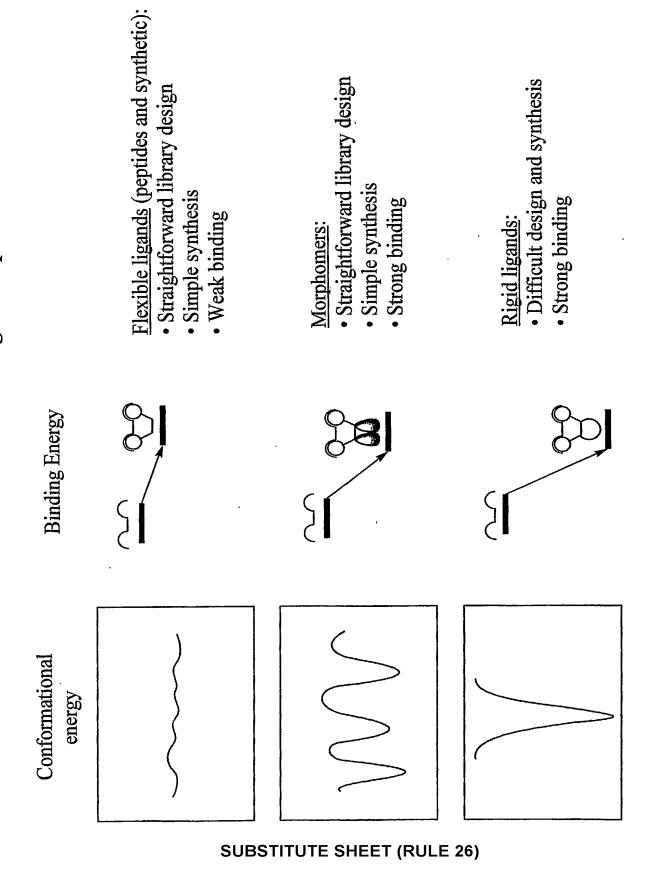


FIGURE 4

General Strategy of Small Molecules – 8-Sheet breakers for Therapy of Alzheimer's Disease by mass spectrometry solubilization assay + analysis of hits Fluorescent AB complementation 3. Screening **B-Galactosidase** In vivo HTS In vitro assay Scaffold synthesis generation 2. Library Morphomer concept focused design of components ibraries of small molecules – capable of crossing BBB Know-how Bioavailability: **B-sheet breakers** structural design 1. Design: Proprietary

SUBSTITUTE SHEET (RULE 26)

Screening of Small Molecules for AB Solubilization Activity

In vivo

In vitro

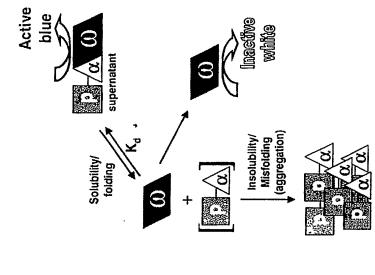
• Fluorescent Assay:

Aβ fiber stained with Thioflavin T solubilization/depolymerization is monitored by fluorescence decrease

· Mass spectrometry assay:

Complexes of amyloid with small molecules are detected and characterized by MS

Hits are fully structurally characterized using regiochemical taggig techniques (provisional patent application filed)



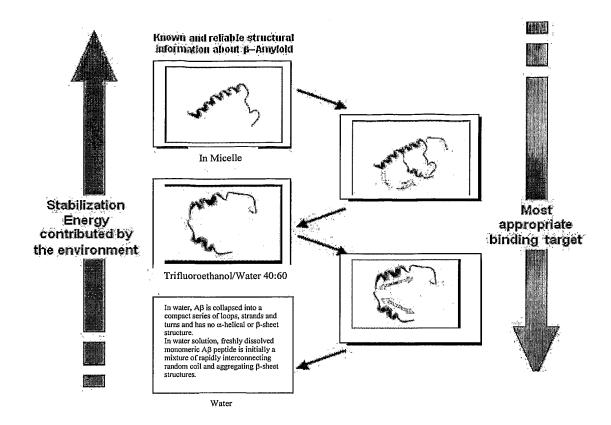
in vivo solubilization assay for Aβ (W.C. Wigley, et al. Nature Biotechnol. 2001, 19, 131-136)

pellet

FIGURE 5

SUBSTITUTE SHEET (RULE 26)

Figure 6



WO 2005/081897 PCT/US2005/005381 7/9

Figure 7

Molecular Design

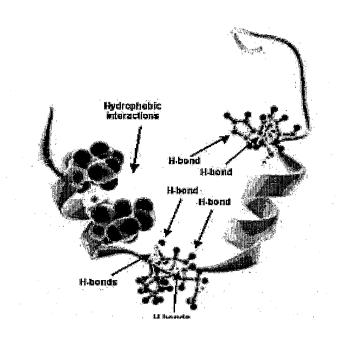


Figure 8

 \mathbf{A}

B

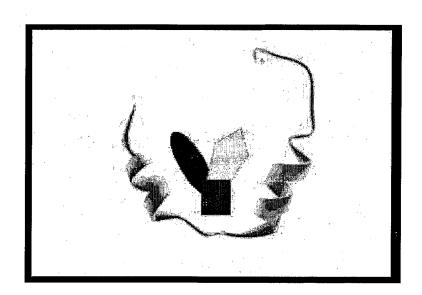


Figure 9